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## **Developing strategies for predicting hyperkalemia in potassium-increasing drug-drug interactions**

Eschmann, Emmanuel ; Beeler, Patrick Emanuel ; Schneemann, Markus ; Blaser, Jürg

**Abstract:** **OBJECTIVE:** To compare different strategies predicting hyperkalemia (serum potassium level 5.5 mEq/l) in hospitalized patients for whom medications triggering potassium-increasing drug-drug interactions (DDIs) were ordered. **MATERIALS AND METHODS:** We investigated 5 strategies that combined prediction triggered at onset of DDI versus continuous monitoring and taking into account an increasing number of patient parameters. The considered patient parameters were identified using generalized additive models, and the thresholds of the prediction strategies were calculated by applying Youden's J statistic to receiver operation characteristic curves. Half of the data served as the calibration set, half as the validation set. **RESULTS:** We identified 132 incidences of hyperkalemia induced by 8413 potentially severe potassium-increasing DDIs among 76 467 patients. The positive predictive value (PPV) of those strategies predicting hyperkalemia at the onset of DDI ranged from 1.79% (undifferentiated anticipation of hyperkalemia due to the DDI) to 3.02% (additionally considering the baseline serum potassium) and 3.10% (including further patient parameters). Continuous monitoring significantly increased the PPV to 8.25% (considering the current serum potassium) and 9.34% (additional patient parameters). **CONCLUSION:** Continuous monitoring of the risk for hyperkalemia based on current potassium level shows a better predictive power than predictions triggered at the onset of DDI. This contrasts with efforts to improve DDI alerts by taking into account more patient parameters at the time of ordering.

DOI: <https://doi.org/10.1093/jamia/ocw050>

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ZORA URL: <https://doi.org/10.5167/uzh-124074>

Journal Article

Published Version

Originally published at:

Eschmann, Emmanuel; Beeler, Patrick Emanuel; Schneemann, Markus; Blaser, Jürg (2017). Developing strategies for predicting hyperkalemia in potassium-increasing drug-drug interactions. *Journal of the American Medical Informatics Association (JAMIA)*, 24(1):60-66.

DOI: <https://doi.org/10.1093/jamia/ocw050>

## Research and Applications

# Developing strategies for predicting hyperkalemia in potassium-increasing drug-drug interactions

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Received 26 October 2016; Revised 4 March 2016; Accepted 12 March 2016

## ABSTRACT

**Objective:** To compare different strategies predicting hyperkalemia (serum potassium level  $\geq 5.5$  mEq/l) in hospitalized patients for whom medications triggering potassium-increasing drug-drug interactions (DDIs) were ordered.

**Materials and Methods:** We investigated 5 strategies that combined prediction triggered at onset of DDI versus continuous monitoring and taking into account an increasing number of patient parameters. The considered patient parameters were identified using generalized additive models, and the thresholds of the prediction strategies were calculated by applying Youden's J statistic to receiver operation characteristic curves. Half of the data served as the calibration set, half as the validation set.

**Results:** We identified 132 incidences of hyperkalemia induced by 8413 potentially severe potassium-increasing DDIs among 76 467 patients. The positive predictive value (PPV) of those strategies predicting hyperkalemia at the onset of DDI ranged from 1.79% (undifferentiated anticipation of hyperkalemia due to the DDI) to 3.02% (additionally considering the baseline serum potassium) and 3.10% (including further patient parameters). Continuous monitoring significantly increased the PPV to 8.25% (considering the current serum potassium) and 9.34% (additional patient parameters).

**Conclusion:** Continuous monitoring of the risk for hyperkalemia based on current potassium level shows a better predictive power than predictions triggered at the onset of DDI. This contrasts with efforts to improve DDI alerts by taking into account more patient parameters at the time of ordering.

**Key words:** clinical decision support, drug-drug interactions, hyperkalemia, monitoring, potassium

## BACKGROUND AND SIGNIFICANCE

Drug-drug interactions (DDIs) are a significant cause of adverse drug events (ADEs) leading to increased morbidity and mortality.<sup>1,2</sup> Although most DDIs are preventable, up to 28% of inpatients suffer from DDI-induced ADEs.<sup>3</sup>

It has been suggested that clinical decision support (CDS) can intercept the ordering of medications triggering DDIs.<sup>4,5</sup> While some authors have pointed out that DDI alerts may prevent ADEs,<sup>6</sup> so far no study has shown that CDS significantly reduces the frequency of ADEs. In particular, alert override rates of up to 98% hamper the

potential of CDS interventions.<sup>7,8</sup> One reason for nonadherence is the low specificity and clinical insignificance of electronic alerts.<sup>9</sup> Therefore, electronic warnings displayed for patients with a low risk for developing respective ADEs should be suppressed.<sup>8–11</sup>

Approaches to increase the alert specificity involve focusing on high-priority DDIs or on tiering DDIs by severity,<sup>12–14</sup> considering patient factors and comedication in order to suppress insignificant alerts,<sup>15</sup> and using a combination of these approaches.<sup>9,16–18</sup> On the one hand, patient factors are typically considered only at the time of ordering; on the other hand, conditions that later change may critically influence the risk that an ADE occurs.<sup>9,15,16</sup> Therefore, sophisticated algorithms taking into account the change of dynamic patient parameters over time have been advocated.<sup>17–20</sup> A promising approach to improving medication safety may be to display warnings as soon as an ADE is imminent or likely to occur, instead of undifferentiated alerts at the time of ordering. However, to our knowledge, no comparison of predictions of ADEs triggered at the time of ordering with serial predictions based on continuous monitoring has been published so far.

We undertook this comparison study using retrospective data on potassium-increasing DDIs. These DDIs occur in up to 10% of hospitalized patients.<sup>1,3</sup> Hyperkalemia is found in 1.9% of these DDIs<sup>21</sup> and can induce life-threatening cardiac arrhythmias.<sup>22</sup> To our knowledge, the number of hyperkalemia cases due to avoidable potassium-increasing DDIs has not been quantified so far, and therefore we also included the results of this prerequisite in our results section.

## OBJECTIVE

To model and compare different strategies predicting hyperkalemia in hospitalized patients for whom medications triggering potassium-increasing DDIs were ordered.

## MATERIALS AND METHODS

### Setting

The University Hospital Zurich, Switzerland, is a tertiary care academic medical center with 850 beds and approximately 35 000 admissions per year. We included data on all inpatients from December 1, 2009, to December 31, 2011. Patients undergoing dialysis and those hospitalized in intensive care units were excluded.

The local research ethics committee approved the analyses, and patient consent was waived.

### Analysis of patient parameters

We analyzed the following patient parameters potentially influencing serum potassium ( $K^+$ ) level: age, gender, medications (severity level of potassium-increasing DDI, duration of potassium-increasing DDI, number of concurrent potassium-increasing drugs, number of concurrent potassium-decreasing drugs), recent blood transfusion, comorbidities (kidney failure expressed by glomerular filtration rate, kidney transplant, diabetes mellitus, hypertension, heart failure, lung transplant), the unit (surgical versus nonsurgical specialties), most recent serum  $K^+$  within 48 hours prior to the onset of the DDI (baseline  $K^+$ ), and the temporal change of the serum  $K^+$  level during the DDI.<sup>21</sup>

### DDIs and potassium-increasing drugs

DDIs were identified using the knowledge base galdat/hospINDEX (distributed by e-mediast AG, Berne, Switzerland; derived from

ABDATA Pharma-Daten Service, Werbe- und Vertriebsgesellschaft Deutscher Apotheker, Eschborn, Germany), which tiers DDIs into 6 levels of severity.<sup>23</sup> Levels 1–3 categorize severe DDIs (1: recommendation “contraindicated,” 2: “contraindicated as precaution,” 3: “monitoring or adaptation required”) and were considered in the present study, whereas levels 4–6 were excluded (4: “monitoring or adaption in case of risk factors,” 5: “monitoring as a precaution,” 6: “no action required”).

Potassium-increasing drugs were defined as drugs involved in severe potassium-increasing DDIs, including angiotensin-converting enzyme (ACE) inhibitors, angiotensin antagonists (angiotensin-receptor blockers), direct renin inhibitors, immunosuppressive agents (calcineurin inhibitors), potassium-sparing diuretics (aldosterone-receptor antagonists and epithelial sodium channel blockers),  $K^+$  supplements, and trimethoprim (ingredient of co-trimoxazole).

### Hyperkalemia

Hyperkalemia was defined as serum  $K^+$  level  $\geq 5.5$  mEq/l.<sup>24</sup> Each case of hyperkalemia was verified by chart review, and cases with documented measurement issues, such as incorrect blood sampling or incorrect handling, were excluded. In addition, corrective actions taken by the health care professionals were recorded and compared to the best therapeutic options on a case-by-case basis.<sup>25</sup> Only occurrences of hyperkalemia detected during potassium-increasing DDIs were reviewed. The chart review was performed by an experienced internist (M.S.).

### Modeling of prediction strategies

We modeled 5 prediction strategies (labeled P; Figure 1), comparing their strength to correctly predict the occurrence of hyperkalemia during potassium-increasing DDIs. Data from patients already presenting with hyperkalemia at the onset of the DDI were excluded.

The three  $P_{\text{initial}}$  prediction strategies were triggered only once, at the onset of the potassium-increasing DDI. Thus, they predicted the risk of hyperkalemia for the entire DDI period (referred to as “long-term predictions”). These  $P_{\text{initial}}$  strategies took into account a step-wise increasing number of factors influencing the serum  $K^+$  level:

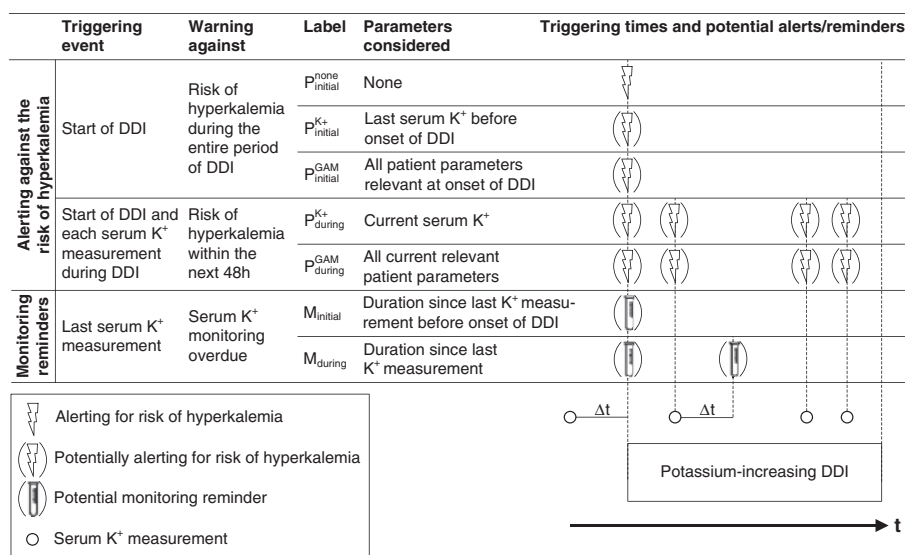
- i. no parameter at all ( $P_{\text{initial}}^{\text{none}}$ ),
- ii. the baseline serum  $K^+$  level ( $P_{\text{initial}}^{K^+}$ ), and
- iii. all patient factors significantly influencing the  $K^+$  level ( $P_{\text{initial}}^{\text{GAM}}$ ) according to prior work.<sup>21</sup>

In contrast, both  $P_{\text{during}}$  prediction strategies were triggered not only at the onset of the DDI, but again for each serum  $K^+$  level measured during the DDI. These strategies predicted the risk of hyperkalemia for the next 48 hours (referred to as “short-term predictions”) and considered

- iv. merely the current serum  $K^+$  level ( $P_{\text{during}}^{K^+}$ ), versus
- v. all patient parameters affecting the serum  $K^+$  progress ( $P_{\text{during}}^{\text{GAM}}$ ).

The patient data were split into a calibration set (used for building the strategies) and a validation set (used for validating the strategies) by applying a sample cube method<sup>26</sup> in order to generate robust models and avoid overfitting. A balanced distribution was obtained by splitting the patients considering a balanced allocation of patient factors influencing the serum  $K^+$  level.

The calibration was performed depending on the prediction strategy. For strategy “ $P_{\text{initial}}^{K^+}$ ” the threshold for predicting hyperkalemia was calculated by applying Youden’s J statistic to a receiver operation characteristic (ROC) curve built on the baseline serum  $K^+$  level.<sup>27</sup>



**Figure 1.** Design of alert and reminder strategies

**Table 1.** Observed versus preferred actions following the 132 hyperkalemic  $K^+$  levels measured during potassium-increasing drug-drug interactions

Actions	Observed <sup>a</sup> (%)	Preferred <sup>b</sup> (%)
Modifying the drug order of $\geq 1$ interacting drug	47 (43.2)	132 (100.0)
Discontinuing $\geq 1$ interacting drug	26 (19.7)	36 (27.3)
Switching $\geq 1$ interacting to another drug	0 (0.0)	89 (67.4)
Pausing $\geq 1$ interacting drug	31 (23.5)	7 (5.3)
Starting potassium-decreasing therapy	62 (47.0)	112 (84.8)
No measures taken	39 (29.5)	0 (0.0)

<sup>a</sup>Actions observed within 24 h of hyperkalemic  $K^+$  level measurements. The actions consist of modifications of actual potassium-increasing drug orders and/or beginning potassium-decreasing therapy.

<sup>b</sup>Action recommended by expert based on chart review.

$K^+$ : serum potassium level.

Strategy “ $P_{\text{during}}^{K^+}$ ” additionally took into account all  $K^+$  levels measured during the DDI period (followed by at least 48 hours of unchanged potassium-increasing drug orders). “ $P_{\text{initial}}^{\text{GAM}}$ ” was modeled using a generalized additive model (GAM): this algorithm selected those parameters at the onset of the DDI that were most predictive for calculating the long-term risk of developing hyperkalemia.<sup>28</sup> The threshold was again defined by applying Youden’s J statistic to the resulting ROC curve. For “ $P_{\text{during}}^{\text{GAM}}$ ” the GAM took into account all patient parameters that were predictive for the short-term risk of developing hyperkalemia.

The ROC areas under the curve were compared with DeLong’s test,<sup>29</sup> and the *P*-value was adjusted with Hommel’s method.<sup>30</sup>

For the validation of “ $P_{\text{initial}}$ ” predictions, subsequent hyperkalemia was defined as hyperkalemia occurring any time during the DDI. In contrast, for the validation of “ $P_{\text{during}}$ ” predictions, imminent hyperkalemia was defined as hyperkalemia occurring between the current time and the next 48 hours. In order to give equal weight to each patient and the respective parameters, the validation of the prediction strategies considered only the first event (subsequent risk of or occurrence of hyperkalemia) per patient.

### Hypothetical monitoring reminders

We added 2 hypothetical monitoring reminders (labeled M; Figure 1) to foster periodic serum  $K^+$  measurements, a prerequisite for the prediction strategies studied:  $M_{\text{initial}}$ , ensuring that a recent serum  $K^+$  level was known at the onset of the DDI, and  $M_{\text{during}}$ , encouraging regular serum  $K^+$  monitoring.

The number of hypothetical monitoring reminders required was calculated using the same validation set as the one used to validate the prediction strategies. The analysis was carried out with 2 different intervals: the short monitoring interval of 48 hours was adopted from our previous study, which showed that monitoring intervals exceeding 48 hours during potassium-increasing DDIs were associated with a higher risk for hyperkalemia<sup>21</sup>; the other defined interval was 72 hours in order to investigate a potential reduction in the number of hypothetical monitoring reminders.

### Statistical analyses

Data analyses, model constructions, and statistical tests were performed using the R language and environment for statistical computing, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). The R package “sampling” was used to split the data into calibration and validation sets, “pROC” to plot ROC curves, and “mboost” to model and validate GAMs.  $P \leq .05$  were considered to be statistically significant.

## RESULTS

We analyzed the data on 76 467 inpatients (mean age 49.6 years, 50.3% female) for whom a total of 1 543 578 drugs were prescribed, including 77 799 potassium-increasing drugs (5.0%). They resulted in 8413 potentially severe potassium-increasing DDIs concerning 5637 inpatients (mean age 65.8 years, 31.3% female).<sup>21</sup> Of those patients, 90 developed a total of 132 hyperkalemic events during the DDIs.

The chart reviews to record the measures taken after these hyperkalemic events revealed that more than half of the DDIs remained unchanged, although a number of corrective actions should have been taken (Table 1). The finding that only half of the orders were

**Table 2.** Evaluation of strategies predicting hyperkalemia in potassium-increasing drug-drug interactions

Label	Model calibration Parameters used	ROC AUC	ROC AUC comparison (p) <sup>b</sup>	Model validation <sup>a</sup>									
				Alerts <sup>c</sup>	TP	FP	FN	TN	Sens. (%)	Spec. (%)	PPV (95% CI) (%)	NPV (%)	
P <sub>initial</sub> <sup>none</sup>	None	–	–	1619	29	1590	0	0	100.0	0.0	1.79 (1.20, 2.56)	–	
P <sub>initial</sub> <sup>K<sup>+</sup></sup>	Last K <sup>+</sup> before onset of DDI ≥ 4.3 mEq/l	0.603	–	398	12	386	17	1192	41.4	75.5	3.02 (1.57, 5.21)	98.8	
P <sub>initial</sub> <sup>GAM</sup>	7 patient parameters: last K <sup>+</sup> before onset of DDI, GFR, number of potassium-in- creasing drugs, number of potassium-decreasing drugs, blood transfusion, age, clinic	0.786	vs P <sub>initial</sub> <sup>K<sup>+</sup></sup> (0.067)	387	12	375	16	1105	42.9	74.7	3.10 (1.61, 5.35)	98.6	
P <sub>during</sub> <sup>K<sup>+</sup></sup>	Current K <sup>+</sup> ≥ 4.5 mEq/l	0.839	vs P <sub>initial</sub> <sup>K<sup>+</sup></sup> (0.007*)	303	25	278	13	1133	65.8	80.3	8.25 (5.41, 11.94)	98.9	
P <sub>during</sub> <sup>GAM</sup>	5 patient parameters: current K <sup>+</sup> , severity level of DDI, number of potassium-in- creasing drugs, number of potassium-decreasing drugs, duration since onset of DDI	0.841	vs P <sub>initial</sub> <sup>GAM</sup> (0.770)	289	27	262	7	756	79.4	74.3	9.34 (6.25, 13.30)	99.1	
			vs P <sub>initial</sub> <sup>K<sup>+</sup></sup> (0.006*)										
			vs P <sub>initial</sub> <sup>GAM</sup> (0.735)										
			vs P <sub>during</sub> <sup>K<sup>+</sup></sup> (0.976)										

<sup>a</sup>In order to give equal weight to each patient and to his or her specific set of parameters, the validation assessed only the first event per patient (either alert or hyperkalemic event).

<sup>b</sup>Calculated on the basis of DeLong's test for comparison; subsequently corrected with Hommel's method for adjustment of p values for multiple comparisons.

<sup>c</sup>Numbers of hypothetical alerts calculated by simulations using data from the validation set.

ROC AUC: area under the receiver operating characteristic curve.

TP: true positive; FP: false positive; FN: false negative; TN: true negative; Sens.: sensitivity; Spec.: specificity; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval; GFR: glomerular filtration rate; \*: statistically significant.

modified after a hyperkalemic event despite the fact that this would have been appropriate for all cases documents the need to alert the physician in charge when hyperkalemia has occurred.

The 5 prediction strategies investigated are presented in Figure 1. Three of them, the P<sub>initial</sub> predictions, were triggered at the onset of each potassium-increasing DDI only. The risk of hyperkalemia was calculated for the entire period of the DDI (long-term predictions), taking into account an increasing number of parameters influencing the serum K<sup>+</sup> level. The 2 P<sub>during</sub> predictions were additionally triggered for each serum K<sup>+</sup> level measured during the DDI, and calculated the risk of hyperkalemia for the next 48 hours (short-term predictions).

The predictive power of the strategies divides them into 2 categories (Table 2). The short-term predictions of hyperkalemia (P<sub>during</sub>) featured a significantly higher positive predictive value (PPV) than the long-term predictions (P<sub>initial</sub>). In contrast, within the 2 categories, there was only a trend of predictive strength between the strategies: The long-term PPV insignificantly increased from "P<sub>initial</sub><sup>none</sup>" through "P<sub>initial</sub><sup>K+</sup>" to "P<sub>initial</sub><sup>GAM</sup>". Also, a trend of the PPV was observed between the short-term predictions from "P<sub>during</sub><sup>K+</sup>" to "P<sub>during</sub><sup>GAM</sup>". The increase of the predictive power is reflected by the ROC AUC: both strategies using short-term predictions performed significantly better compared to the long-term prediction "P<sub>initial</sub><sup>K+</sup>".

The ROC of "P<sub>during</sub><sup>K+</sup>" illustrates the tradeoff between specificity and sensitivity in the function of the threshold value (Figure 2). The superimposed ROC curves of all 5 strategies (Figure 3) show that the short-term predictions "P<sub>during</sub><sup>K+</sup>" and "P<sub>during</sub><sup>GAM</sup>" have similar curves and perform better than the long-term predictions "P<sub>initial</sub>".

We added hypothetical K<sup>+</sup> monitoring reminders to the prediction strategies to ensure that K<sup>+</sup> levels would be available to the

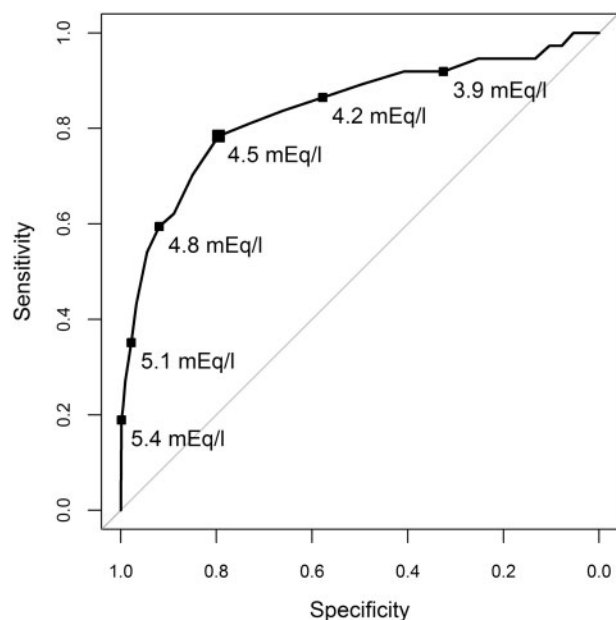
prediction models (Figure 1).<sup>31</sup> The simulation of the required monitoring reminders showed that medications triggering potassium-increasing DDIs were ordered without knowledge of the current serum K<sup>+</sup> level in 12–15% of the patients (time intervals of 72 and 48 hours, respectively; Table 3). Considering the K<sup>+</sup> monitoring during the entire duration of the DDIs, serum K<sup>+</sup> was not measured within monitoring intervals of 72 hours in 22% and 48 hours in 36% of the patients.

Table 4 illustrates the potential alert burden by summarizing the number of hypothetical monitoring reminders and the number of hypothetical alerts warning against the risk of hyperkalemia according to the 5 strategies analyzed.

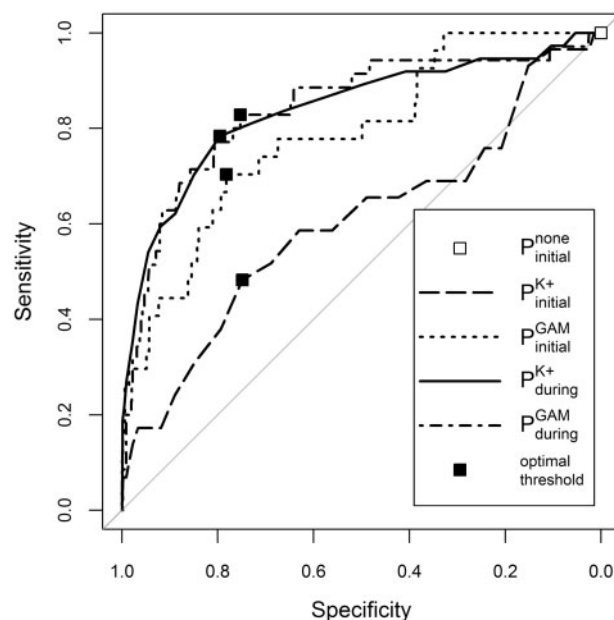
## DISCUSSION

The goal of the study was to evaluate and compare 5 distinct strategies in terms of their ability to predict the risk of hyperkalemia during potassium-increasing DDIs in order to prevent hyperkalemia by means of alerts. Our analysis shows that short-term predictions, similar to continuous monitoring of DDIs, perform significantly better than long-term predictions exclusively triggered at the onset of potassium-increasing DDIs.

Besides providing up to 3 times higher PPVs, the switch from long-term to short-term predictions also improved the ROC AUC of the respective strategies, increasing the sensitivity but still decreasing the potential alert burden. Of note, only short-term predictions achieved sensitivity of nearly 70%, a sensitivity considered to be adequate.<sup>32</sup> In contrast, taking into account further patient parameters affecting the development of hyperkalemia showed only a modest



**Figure 2.** Receiver operating characteristic curve of prediction strategy  $P_{\text{K}^+}^{\text{during}}$  predicting hyperkalemia for the next 48 hours based on the current serum potassium level.



**Figure 3.** Comparison of receiver operating characteristic curves of all evaluated prediction strategies

**Table 3.** Numbers of hypothetical reminders for different serum  $K^+$  monitoring strategies during potassium-increasing DDIs

$\Delta t$	Reminders at onset of DDI <sup>a</sup>		N (% <sup>b</sup> )	Reminders at onset of and during DDI <sup>a</sup>		N (% <sup>b</sup> )
	Label	Trigger		Label	Trigger <sup>c</sup>	
48 h	$M_{\text{initial}}^{48\text{h}}$	If no $K^+$ level is available within 48 h prior to the onset of the DDI	154 (15)	$M_{\text{during}}^{48\text{h}}$	If no $K^+$ level is available within 48 h prior to the current check	375 (36)
72 h	$M_{\text{initial}}^{72\text{h}}$	If no $K^+$ level is available within 72 h prior to the onset of the DDI	123 (12)	$M_{\text{during}}^{72\text{h}}$	If no $K^+$ level is available within 72 h prior to the current check	231 (22)

<sup>a</sup>In order to allow for comparison with Table 2, only the first event per patient was assessed.

<sup>b</sup>Reminders in percentage of the total number of patients included within the validation set.

<sup>c</sup>This condition is continuously tested during the entire period of each potassium-increasing DDI.

gain. Short-term predictions performed better with fewer parameters and thus with lower costs than long-term predictions.

The GAM algorithm selected different patient parameters for the long-term versus short-term prediction strategies: “ $P_{\text{initial}}^{\text{GAM}}$ ” used the last serum  $K^+$  level measured before the onset of the DDI and considered the number of drugs ordered affecting serum  $K^+$  level, kidney function, blood transfusions, age, and the unit. In contrast, “ $P_{\text{during}}^{\text{GAM}}$ ” considered the severity level of the DDI, the previous duration of the DDI, and the number of drugs ordered affecting the serum  $K^+$  level and monitored the current serum  $K^+$  level. However, this is in line with our observation<sup>21</sup> that the severity level is not helpful for long-term predictions of developing hyperkalemia. Of note, the ordering of level 1 DDIs often relates to the correction of hypokalemia, and this intentional treatment appears to be less likely to induce hyperkalemia, possibly due to closer serum  $K^+$  monitoring by the health care professionals in charge.

Serial predictions of the risk for hyperkalemia during potassium-increasing DDIs require regularly updated laboratory values. Therefore, there is a need to increase  $K^+$  monitoring by providers. Such monitoring reminders may increase the alert burden, potentially undermining the aim to reduce the number of displayed

notifications. However, an innovative approach mitigating this issue would be the automated generation of  $K^+$  measurement orders, and monitoring reminders would then no longer be necessary.

If our described strategies were implemented in an electronic health record as automated notifications, both alerts warning against the risk of hyperkalemia and monitoring reminders, could unobtrusively make recommendations to providers at the time of order entry. Also, alerts and monitoring reminders triggered during the DDI could be displayed in a noninterruptive manner, such as in the overview of current medication orders or laboratory results. Overdue serum  $K^+$  measurements could be prefilled automatically in laboratory order forms. The alerts warning against the risk of hyperkalemia described above should be complemented by actual hyperkalemia alerts (serum potassium level  $\geq 5.5$  mEq/l). These supplementary alerts would draw the physician’s attention to the fact that the chosen drug therapy may aggravate the already present hyperkalemia.

Our study has several limitations. First, the data were obtained from a single site, which may limit the generalizability of the findings. In this context, the high proportion of multimorbid patients and the frequent monitoring of laboratory results at our institution may have influenced the model thresholds, which should be



**Table 4.** Number of hypothetical alerts warning against the risk for hyperkalemia and of hypothetical potassium monitoring reminders

Triggering event	Alerts		Reminders		Total <sup>a</sup>
	strategy	N	strategy	N	
Start of DDI	p <sub>none</sub> <sup>initial</sup>	1619	–	0	1619
	p <sub>K<sup>+</sup></sub> <sup>initial</sup>	398	M <sub>initial</sub> <sup>72h</sup>	123	521
	p <sub>initial</sub> <sup>GAM</sup>	387	M <sub>initial</sub> <sup>72h</sup>	123	510
Start of DDI and each serum K <sup>+</sup> measurement during DDI	p <sub>during</sub> <sup>K<sup>+</sup></sup>	303	M <sub>during</sub> <sup>72h</sup>	231	534
	p <sub>during</sub> <sup>GAM</sup>	289	M <sub>during</sub> <sup>72h</sup>	231	520

<sup>a</sup>Sum of number of alerts plus number of reminders.

validated on site before being used in other institutions. Nevertheless, the described predictions can easily be implemented at other institutions, since the proposed strategies have been disclosed in detail. Second, only a single expert reviewed the patient charts to retrospectively assess treatment options following hyperkalemic events. Third, we assumed that the consequences of false positive and false negative alerts were comparable. We therefore calculated the alert threshold using the optimality criterion of Youden's J statistic, giving equal weight to specificity and sensitivity. At any rate, CDS interventions incorporating such predictions could take into account stakeholder preference for specificity or sensitivity. Fourth, a PPV <10% may appear insufficient, but this has to be interrelated with the low frequency of hyperkalemia during potassium-increasing DDIs (1.9%).<sup>21,33</sup>

Various approaches to improve the specificity of DDI alerts have been proposed, including focusing on high-priority DDIs,<sup>12</sup> tiering DDIs by severity,<sup>13,14</sup> taking into account patient factors and comedications,<sup>15</sup> considering the change of conditions over time,<sup>19</sup> or using a combination of these strategies.<sup>9,16–18</sup> However, the effects of these approaches have rarely been quantified. Paterno et al.<sup>13</sup> demonstrated that tiering DDI alerts by severity increased compliance by 19%. Helmons et al.<sup>18</sup> reduced the number of alerts by 55% by focusing on high-priority DDIs and considering critical patient parameters 3 times a day.

To our knowledge, this is the first study comparing prediction strategies triggered exclusively at the onset of potassium-increasing DDIs (long-term predictions) with serial prediction recalculations throughout the duration of DDIs (short-term predictions). Our observation that the predictive power of alerts can be improved by focusing on short-term predictions may positively influence the crucial efforts to reduce the alert burden, which in turn would minimize the risk for alert fatigue. Furthermore, this approach may be of importance for various other categories of prescription warnings, provided that the risk of potential ADEs can be monitored.

Finally, predictions recalculated throughout the duration of DDIs can be combined with human factors principles.<sup>34–39</sup> For instance, the models presented could generate alerts with graduated priorities as a function of the alert threshold, such as medium risk notifications versus warnings against a high risk of imminent hyperkalemia. Finally, since alerting at the appropriate time is a central

aspect of human factors principles, short-term predictions constitute a novel and important approach to address human factors.

## CONCLUSION

In conclusion, our findings show that continuous monitoring of the risk for hyperkalemia based on current potassium level shows a better predictive power than predictions triggered at the onset of DDI. This contrasts with efforts of improving DDI alerts by taking into account more detailed patient data at the time of ordering, whereas algorithms continuously monitoring only the prime patient parameter likewise perform well.

## CONTRIBUTIONS

E.E. designed and performed the research, analyzed, and interpreted data, and wrote the manuscript.

M.S. contributed to the research, assessed patient history, interpreted data, and edited the manuscript.

P.B. contributed to the research, interpreted data, and edited the manuscript.

J.B. designed the research, interpreted data, and edited the manuscript.

All authors approved the manuscript.

## FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

## COMPETING INTERESTS

The authors declare that they have no conflict of interest.

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